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OLD AND NEW IN GENETICS

L. C. DUNN

Senior Research Scientist, Columbia University
Nevis Biological Station, Irvington-on-Hudson, N. Y.

MANY periods of change in scientific knowledge have been referred to as revolutions. In biology the major change was often called the Darwinian revolution. In the succession of events leading to genetics, the Mendelian revolution was primary. The roots of this were contemporary with *The Origin of Species*, but its effects were first felt forty years later, beginning in 1900. The development and generalization of the chromosome theory of heredity, led by T. H. Morgan and his associates, occurred in a short space of years, the climax of which was marked by the publication of *The Theory of the Gene* in 1926. In Darwin's case the threat to established authority and the bitter controversies provoked by his book of 1859 gave a radical and revolutionary flavor to a doctrine of evolution by slow change. But in the case of Mendel and the Morgan school it was the rapidity with which new ideas were developed and extended which marked the change. The new was added to the old. This hardly constitutes revolution, although in biological circles it was accompanied by the kind of excitement which is evoked by social and political upheaval. In science, however, such excitement finds its outlet in new research which

increases in volume and scope. This feedback effect enhances the speed of change.

We are now in the midst of a new period of very rapid increase of knowledge of the mechanism of heredity, and it is accompanied by the intense interest and excitement of new discovery. Already we hear the cracking of the genetic code referred to as "revolutionary". The prospect has been opened of viewing the processes of heredity on a molecular level, certainly in a more general and elementary way than had ever been possible before. Even though "revolution" may not be the appropriate word for this or any other scientific development, still its use should cause us to reflect on the nature of the change which is now occurring. Will established theories of genetics be destroyed? Will the new knowledge cause a radical change in our perception of the problems of genetics as these had taken form in the "classical" period up to say 1945 or 1950? Does the "new genetics" deal with new questions and can the new be added to the old, as happened in the earlier periods of rapid change?

It will help, in the consideration of these questions, if we keep in mind what have been the chief directions of research in classical genetics. In broad terms, these have dealt first with the transmission mechanism of heredity, and the physical constitution of the genetic material; second, with heredity and variation (mutation) as these operate in populations and thus with the causes and mechanism of evolution; and third, with the functioning of the genetic material in controlling the metabolism and development or morphogenesis of the individual. These are usually discussed under the rubrics formal genetics (or transmission genetics), population genetics and physiological or developmental genetics. These are obviously distinctions of convenience for purposes of study by different methods adapted to the analysis of different questions; but it should be clear that all seek to understand a single entity, the succession of living organisms in reproduction, heredity, evolution and individual development.

The chief focus through which these problems came to be viewed was the concept of the gene. This was a statistical concept resting at first simply on the occurrence of Mendelian segregation and assortment, later becoming an element in a logical system of linkage groups, inferred from breeding analysis, subsequently to be associated with individual chromosomes by cytogenetic methods in the 1920's and

1930's. Although some cases of transmission by nonchromosomal elements were known, it was concluded that by and large the problem of the transmission system of heredity had been solved when it had been shown to consist of genes which could be assigned to a linear system of bead-like loci in the chromosomes.

It could in fact be said that the problem of the transmission system has been solved three times: once by the discovery of the statistical gene, once by the proof of the beads-on-a-string theory, and now by the proof that the genetical material consists of a linear sequence of base-pairs, the order in which these are arrayed in a polynucleotide corresponding to a specific instruction for the synthesis of an amino acid and thus of part of a polypeptide chain of a protein. Each claim to a solution is justified, for each had answered the question which had been asked. Progress came from the ability to ask new questions and from the development of new methods.

The "middle solution", i.e. *The Theory of the Gene*, as stated by Morgan, was explicitly restricted to the transmission system: "The theory of the gene, as here formulated, states nothing with respect to the way in which the genes are connected with the end-product or character" (p. 26), and "the only properties ascribed to the gene are those given in the numerical data supplied by the individuals" (p. 27).

But it was obvious that the constitution of the genetic transmission system could not be understood except as a result of a process of evolution guided by natural selection. The elements of heredity, whether they be considered as single nucleotides or as higher orders of pattern in the arrangement of such elements (genes, cistrons) are not merely parts of individual organisms but of continuous lines of descent which constitute the populations in both time and space out of which races, species and higher taxonomic categories are constituted. The thousands of separable elements could appear in a huge number of combinations and the action of natural selection would lead to the disproportionate multiplication and transmission of those combinations which were internally harmonious and adjusted to their environments.

This view of the genetic system as a part of a continuum led, as soon as the gene concept took form, to two essential questions: How does the gene reproduce itself, and how do new and different gene forms arise? Classical genetics was unable to give more than a formal

description of the first process. What it learned about gene reproduction came chiefly from experimental studies of the second question, that of mutation initiated by de Vries at the end of the 19th century and carried forward with great brilliance and persistence chiefly by H. J. Muller. He proved that the change of a gene from one alternative form (allele) to another was a random one; but that the frequency with which it occurred could nevertheless be altered by application of energy such as x-radiation. Even the later proof by Auerbach and others, that mutations could be induced by chemical treatments, did not reach the goal of achieving direction or control of a process which was now known to be subject to some kind of molecular mistake in the copying of a parental by a descendant gene. But the work on experimental production of mutations revealed what to look for. In the year following Muller's demonstration of artificial transmutation of the gene (1927), a new clue appeared from an unsuspected source, Griffith's discovery of the transfer of specific transforming material from one bacterium to another. When Avery, MacLeod and McCarty proved in 1944 that the material transferred was deoxyribose nucleic acid, thereby identified as the specific hereditary material competent to transmit a new hereditary property without sexual crossing, then a new kind of genetics began.

It was proper to call this molecular genetics since the problems of continuity and change could now be asked in molecular terms. Specifically, they became problems of DNA structure, transmission, and function in producing the hereditary characters of organisms. This substance, usually in association with protein, is found in chromosomes wherever they occur, and has proved to be the transmitter of genetic specificity from generation to generation in all organisms from virus to man, except for a few plant viruses in which the genetic material appears to be ribose nucleic acid. It soon became evident why a nucleoprotein should form the universal basis of heredity; it was able to reproduce its own molecular structure. It thus possessed the essential property of self-reproduction.

In the meantime, beginning in the late thirties, the horizons of classical genetics, which had until then been largely confined to cross-fertilizing plants and animals, including man, were greatly expanded. In filamentous fungi, yeasts, bacteria, and then viruses were found systems of genetical transmission which could be resolved into ele-

ments like genes. These could enter into recombination by methods of reproduction supplementing and sometimes substituting for sexual crossing. It now became possible to test some ideas which had appeared earlier on new and more favorable experimental materials.

Garrod, in the period following the rediscovery of Mendel's principles, had entertained the idea that genes, causing the kinds of diseases which he referred to as "Inborn Errors of Metabolism", produced their effects by blocking specific chemical steps in reaction sequences. The blocks were suspected of being due to failure of gene-operated enzymes. Such a conception was rediscovered in a gene-controlled sequence in Drosophila, but it was the rapidly reproducing bread molds, growing on chemically defined media, which enabled Beadle and Tatum and others to put the one gene–one enzyme hypothesis on its feet, and it was then rapidly exploited in other microorganisms. This led to the view that the primary function of a gene was to impart a specific structure to an enzyme, thus endowing it with a peculiar ability to catalyze one step in a reaction sequence. The old genetics had rather suspected that genes were themselves enzymes and thus proteins; now, the threshold of a new problem came to view, how genes, composed not of protein but of nucleic acid, could govern and determine protein synthesis.

In 1947, applications of methods of physical chemistry directly to the study of a protein produced by a mutated gene led Pauling, Itano, Singer and Wells to identify the specific change in the protein brought about by the gene. The discovery of the first of the abnormal human hemoglobins which they described as causing a "molecular disease"–sickle-cell anemia–was followed by the identification of a large number of other proteins, each of which owed its difference from normal structure to a mutated gene. Ingram then showed that the change due to the mutation, in the case of each of two abnormal hemoglobins, was confined to a single amino acid residue at one point in one of the polypeptide chains composing the globin. There could be no doubt that genes controlled protein structure by specifying the sequence of amino acid residues in the polypeptide chains. The assumed basic functional correspondence was then altered from "one gene–one enzyme" to "one gene–one polypeptide."

A major step in the creation of molecular genetics was the proposal by Watson and Crick in 1953 of a model of the molecular structure and manner of replication of DNA. In 1956, the pathway leading

to the biosynthesis of DNA was discovered by Kornberg and his associates who showed how the specific polynucleotide chains of DNA are formed in the cell. This was followed by the solution in broad outline of the problem of how the structure of specific DNA molecules is transmitted to descendant molecules and how this structure is translated into specific protein structure in the descendant cells. This is the so-called "coding" problem of which a brief account will be given shortly.

All of this will be easily recognized as a part of the new genetics. In molecular terms, the gene which had been conceived as an active unitary particle, now was viewed as a segment of a large number of base pairs, possibly hundreds of them, in a chain of thousands of nucleotides distributed in linear order in a chromosome or comparable structure. This resolution of genes, as units controlling specific functions, into linear sequences of subelements, had also been achieved by the usual methods of classical genetics which are breeding experiments often accompanied by cytological examination. This sort of "fine-structure analysis" began when some of the genes of Drosophila and maize were shown to consist of subelements which in rare instances separated by a recombination (crossing over) within the gene-locus. Detecting such rare events required observations on millions rather than on the hundreds or thousands of offspring which had been sufficient for detecting intergenic recombination and for the construction of chromosome maps. These huge populations were available in microorganisms, and the climax of resolution of a gene-locus into its parts was reached in one region (cistron) composing perhaps 1/100 of the genetic map of a bacterial virus, in which Benzer and his co-workers demonstrated a linear order of hundreds of separately detectable sites of mutation. The gene, as Benzer pointed out, had ceased to have its old meaning when applied to the level of fine structure, although it still had meaning when used as the unit which could specify an enzyme.

Here we return for a moment to the assumed structure of DNA. Each of its two complementary chains was conceived as consisting of a succession of nucleotides, each consisting of a nitrogen-containing base—a pyrimidine or a purine, a pentose sugar and phosphoric acid. The peculiar and pregnant feature of the model was the relationship between the bases, a purine on one chain, A (adenine) always being bound by a hydrogen bond to a specific pyrimidine T (thymine) on

the other and G (guanine) always bound to C (cytosine). The order of the bases, e.g. A C G T or any variant of the order of these four elements in one strand, was to specify its own genetic effect, i.e. the instructions or information it was to transmit to the cells in which it occurred, particularly what kinds of enzymes they were to produce. It was also to determine the replication of this order when at chromosome replication or copying a daughter strand was assembled out of compounds available in the cell. Since an A base would always choose a T base as its partner, and C associate with G, the result would be the construction of a complementary linear sequence in the daughter strand, thus preserving the order of bases. This order would be the feature determining the continuity of genetic properties, that is, the essence of heredity. The kinds of departures from this order which might arise by mistakes in replication were suggested by the discovery that the change in a protein caused by a mutation was the change in one amino acid residue out of hundreds. If it should prove that the incorporation of each of the 20 amino acids which enter into a protein is governed by some specific sequence of base pairs in the DNA molecule, and that mutation is essentially a change in this sequence, then both maintenance and change of biological properties in reproduction would find an explanation. This, in outline, is what has happened in the last two years. The order of incorporation of amino acids into protein appears to be specified by a code of three-letter words representing the order of base pairs in DNA. The three-letter or triplet code for specifying each of the 20 amino acids is now reasonably well settled. Certainly the general principle is clear. Self-reproduction, the essence of heredity, is the copying of a code of four kinds of nucleotide. The elementary step in mutation, essential for the origination of the variety on which natural selection and other evolutionary forces act, probably results from the miscopying or mispairing of two of the usually complementary pairs, so that a change in base order in a daughter strand results. I have, of course, omitted all reference to the manner in which the code instructions in DNA are transferred via other polynucleotides (RNA) to the ribosomes where enzymes are assembled.

The functions of each enzyme depend precisely upon the arrangement of the many parts of the molecule which would thus be subject to alteration by amino acid substitutions of the sort that could occur

in mispairing in DNA replication. This might occur at any point in the polynucleotide chain of DNA, and recombination or crossing-over between any two adjacent nucleotides might also occur during replication. The work with bacterial viruses shows that mutations can be induced by agents which act on the bases of DNA. The thousands of mutations, both spontaneous and induced, can be localized on a linear map, in which segments having a unit function each consist of hundreds of sites separable by mutation and recombination. This kind of genetic analysis was developed out of the classical concepts and applied with modern refinements to organisms known to consist of DNA. It thus formed a bridge connecting the old with the new in which the analyses of DNA and its relation to protein synthesis have been carried on by chemical and physical procedures often and most profitably in living systems extracted from and devoid of cellular structure.

It is evident now that the two kinds of study, one beginning with the organism, the other with the hereditary material, are going to yield the same kind of picture of heredity and variation. Far from revealing incompatibilities between the traditional and the molecular views of heredity, it seems that work at both levels can now be utilized in attacking the great unsolved problems of evolution and development. The practical benefits of both the new and the old have already been demonstrated in agriculture and medicine, and the tempo of progress in application will certainly now increase as confidence in the empirical knowledge of the genetical transmission system is reinforced as it has been recently.

One contrast between old and new is especially striking although it is not confined to genetics but is now characteristic of "new" science. There was an interval of some forty years between the first publication (1866) of the evidence for the particulate nature of hereditary transmission and its confirmation and extension to bisexual animals and plants generally. Another thirty years passed before it began to affect general biological theories like that of evolution by natural selection (1932); and even after twenty-five more it had not been reconciled with the basic facts of morphogenesis. But now only ten years have elapsed since the first proposal of the model of DNA, and already the code of instructions to descendants which it embodies is recognized as a universal rule not only for inheritance but for the

structure and functioning of living matter.

The older genetics had begun to serve as a focus through which diverse biological problems could be examined and restudied. The new genetics promises to greatly increase the speed with which this will occur over a wider area which will include parts of chemistry and physics as well as biology. It is especially notable that the same methods and attitudes have been successful in dealing with living as with non-living systems. This of course had been shown long ago by the success of general physiology and later by biochemistry, but those sciences had dealt mainly with the stationary or maintenance processes of life. Now it is clear that the advancing processes which are peculiar to living organisms—reproduction, heredity, and evolution—can be dealt with in the same way. One would like to add to this list the problems of the growth and differentiation of the living individual out of a single cell, but at present this would represent a statement of faith rather than accomplishment.